

**REMARKS**

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

**I. CLAIM STATUS & AMENDMENTS**

Claims 7-12 were pending in this application when last examined.

Claims 7-12 were rejected.

Claims 7, 10 and 11 have been amended to delete lidocaine, indomethacin and diclofenac from the Markush groups. Support for these changes can be found in original claims 2-3.

Therefore, no new matter has been added by this amendment.

Claim 12 has been canceled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional application on any canceled subject matter.

Upon entry of this response, claims 7-11 will be pending in this application.

**II. EXAMINER INTERVIEW**

Applicants thank Examiner Isis Ghali for the telephone discussion held with Applicants' representative, Jay F. Williams, to discuss the outstanding obviousness rejections.

During the interview, the Examiner requested a comparison of the claimed skin patch containing 20-60% by weight of water with a prior art composition containing less than 10% to show the criticality of the claimed 20-60% water content. As discussed below, attached herewith is Rule 132 Declaration by Mitsuji Akazawa evidencing the criticality of the claimed 20-60% water content in the present skin patch over a composition containing less than 10%.

### III. REJECTIONS UNDER 35 U.S.C. § 103

#### A. US '363 in view US '874

Claims 7-12 were rejected under 35 U.S.C. § 103(a) as obvious over Mantelle et al., U.S. Patent No. 6,562,363 ("US '363") in view of Oda et al., U.S. Patent No. 5,725,874 ("US '874"). See item 1 on pages 2-5 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims for the same reasons set forth in the section II A on pages 4-5 of the response filed May 20, 2004, and for the following reasons.

According to the amended claims, the external skin patch of the claimed invention comprises, among other ingredients, 20 to 60% by weight of water based upon the total weight of the adhesive gel base.

US '363 and US '874 fail to render obvious the claimed invention, because they fail to disclose and/or suggest this claimed element.

On the other hand, US '363 teaches away from a pharmaceutical composition containing water. In this regard, at column 7, lines 35-44, US '363 discloses that

An important characteristic of the embodiments of the present invention relates to the substantially water-free and water-insoluble nature of the composition. By the term "substantially water-free" is meant that the composition contains less than about 10% by weight water, and preferably less than 5%, and most preferably less than 3% prior to its topical application. In general, it is desirable to avoid the addition of water entirely and to eliminate, as far as possible, the presence of water in the other ingredients of the composition. [Emphasis added]

Based on such disclosure, it is clear that the pharmaceutical formulation of the composition of US '363 is a substantially water-free film or at most, contains less than 10% water. Thus, it is clear that US '363 teaches away from the inclusion of water in the composition, as required by the claimed invention.

It is respectfully submitted that the rejection fails to address this teaching away. As noted in the prior response, it is well established that the prior art must be considered in its entirety and that

references cannot be combined where the references teach away from their combination. See M.P.E.P. § 2145 X, D, 2. There simply can be no motivation where the cited references teach away from the combination. A reference can be said to teach away when a person of ordinary skill in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path taken by the applicant.

In the instant case, one skilled in the art, upon reading US '363, would be discouraged from including water in the topical pharmaceutical skin composition of US '363. Since US '363 teaches away from the inclusion of water (less than 10%), the reference cannot be combined with US '874 to arrive at the claimed invention which is directed to 20 to 60% by weight of water.

In addition, US '363 describes that "this invention relates to compositions capable of being used in wet or moist environments, especially on mucous membranes, for a prolonged period of time." See column 1, lines 13-16 of US '363. This means that the composition of US '363 is intended to be mainly applied to mucous membranes, as opposed to the skin as in the present invention.

Therefore, it is clear that the composition of US '363 is essentially different from the base composition of the external skin patch of the present invention which is an adhesive gel base containing 20 to 60% by weight of water as an essential component. US '363 teaches nothing about a skin patch having a layer containing an adhesive gel base comprising 20% by weight or more of water.

Furthermore, to distinguish the skin patch of the claimed invention containing 20-60% by weight of water content from the substantially water-free film of US '363 (containing less than 10%), the Applicants have conducted experiments as outlined in the attached Rule 132 Declaration by Mitsuji Akazawa ("Akazawa Declaration"). The results of these experiments clearly demonstrate the superior pain relief effect of the present invention. In this sense, the results show that the unexpectedly superior pain relief effect of the present invention cannot be achieved by the skin patch containing less than 10% by weight of water as called for by US '363. Thus, pursuant to the

Examiner's request, the Akazawa Declaration evidences the criticality of the claimed 20-60% water content in the present skin patch over a prior art composition containing less than 10%.

Again, US '363 teaches nothing about a skin patch having a layer containing an adhesive gel base comprising 20% by weight or more of water.

As for US '874, this patent teaches nothing about a composition comprising a polyvinylpyrrolidone polymer as described in US '363. Moreover, the skin patch with substantially-free water of US '363 is entirely different from the skin patch of US '874.

Thus, in addition to the clear teaching away discussed above, there is no motivation to apply the combination of drugs described in US '363 to the preparations disclosed in US '874 to arrive at the claimed invention of an external skin patch which comprises, among other ingredients, 20 to 60% by weight of water based upon the total weight of the adhesive gel base with an expectation of achieving a superior pain relief effect. There simply is no expectation of success as evidenced by the results in the Akazawa Declaration.

Furthermore, notwithstanding that claimed invention is not obvious over the cited prior references, it would have been difficult for one of ordinary skill in the art to discern from the teachings of US '363 and US '874 that an external skin patch of the present invention having a drug reservoir layer which comprises an adhesive gel base containing 20-60% by weight of water and medicinal components containing a specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent can achieve a superior pain relief effect. Please see also the discussion in the prior response regarding the Declaration under 37 C.F.R. § 1.132 by Keiji Nozaki ("Nozaki Declaration") demonstrating that the claimed invention possesses an unexpected synergistic effect in comparison to administration of a random combination of anesthetic or analgesic taught in the prior art. Such unexpected synergistic effects as evidenced by the Akazawa and Nozaki Declarations are indicative of non-obviousness.

In view of the above, the rejection of claims 7-12 under 35 U.S.C. § 103(a) is untenable and should be withdrawn.

**B. US '112 in view US '874**

Claims 7-12 remain rejected under 35 U.S.C. § 103(a) as obvious over Liedtke, U.S. Patent No. 5,686,112 ("US '112") in view of US '874. See item 1 on pages 5-7 of the Office Action.

This ground of rejection is respectfully traversed as applied to the amended claims for the same reasons set forth in the section II A on pages 6-10 of the response filed May 20, 2004 and for the following reasons.

The amended claims call for an external skin patch comprising a specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent, and other ingredients including 20 to 60% by weight of water based upon the total weight of the adhesive gel base. US '112 and US '874 fail to render obvious the claimed invention, because they fail to teach and/or suggest these claimed elements.

The rejection indicates that US '112 suggests a combination of non-steroidal anti-inflammatory analgesics and local anesthetics which are delivered in single dosage topical pharmaceutical form. However, US '112 does not disclose the specific combination of the nonsteroidal antiphlogistic analgesics and local anesthetics of the present invention. Instead, the active compounds described in US '112 are "analgesics and local anesthetics such as buprenorphine, fentanyl, penzocaine, morphine and morphine derivatives, lidocaine, prilocaine, mepivacaine or non-steroidal antirheumatics/antiinflammatories such as indomethacin, diclofenac or etofenamate" See column 3, lines 1-9, and Claims 9-12 in column 6, lines 16-28.

Although analgesics, local anesthetics and non-steroidal anti-rheumatics/anti-inflammatories are described in column 3, lines 1-9 of US '112, the patent does not disclose the specific combinations as claimed, the specific combination of the local anesthetic selected from the group consisting of tetracaine, procaine, dibucaine, benzocaine, xylocaine and pharmaceutically acceptable salts thereof and the nonsteroidal antiphlogistic analgesic agent selected from the group consisting of ketoprofen, piroxicam, felbinac, bufexamac, suprofen, flurbiprofen, ibuprofen and pharmaceutically acceptable salts thereof is not described in US '112.

On the other hand, the medicinal component of the present invention is a specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent. Even if selecting arbitrarily any two compositions each of which is useful for relief pain, a remarkable effect described in the present invention can not necessarily be achieved.

In the previous Response, comparative examples 5-8 and a test example 2 were submitted in the Nozaki Declaration to proof that combinations other than the local anesthetic and the nonsteroidal antiphlogistic analgesic agent of the present invention cannot achieve the remarkable pain relief effect of the claimed invention.

The Nozaki Declaration includes a comparison the claimed combination with the following prior art compositions:

- (a) two analgesics -- diclofenac and indomethacin for Comparative Example 5;
- (b) two anesthetics --lidocaine and xylocaine for Comparative Example 6;
- (c) mixture of an analgesic and a steroidal anti-inflammatory agent -- diclofenac and betamethasone valerate for Comparative Example 7;
- (d) two analgesics -- diclofenac and aspirin for Comparative Example 8.

Note that the combination of a local anesthetic and other analgesics such as aspirin or steroidal ant-inflammatory analgesic agents cannot achieve the unexpectedly superior pain relief effect (see Comparative Examples 7-8).

Further, the pharmaceutical formulation of US '112 is only in semi-solid phase, specifically in cream, emulsion, gel, suspension or ointment form and topical individual doses of the pharmaceutical formulation are situated in individual containers of a molded body.

On the other hand, the pharmaceutical formulation of the present invention is an external skin patch comprising a substrate and a drug reservoir layer which comprises an adhesive gel base comprising a water soluble polymeric material, a crosslinking agent selected from the group consisting of aluminum compounds, water and a humectant selected from the group consisting of polyhydric alcohols, saccharides and superabsorbent resins. Such a composition is an essentially

different art from that disclosed in US '112. US '112 discloses nothing about such external skin patch of the present invention as a pharmaceutical formulation. The technical background of US '112 is entirely different from the present invention.

The Examiner indicates that US '874 discloses a percutaneous preparation comprising a water soluble polymer, humectants such as polyhydric alcohol, water and a crosslinking agent such as aluminum compounds. US '874 also teaches that the examples of a drug comprising the preparation include some non-steroidal ant-inflammatory analgesic agents and local anesthetics.

However, US '874 does not teach anything about the specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent of the present invention.

Since US '874 does not teach anything about such pharmaceutical formulation as described in US '112, and US '112 does not teach anything about such preparation as described in US '874, there is no motivation to apply the drug of US '112 to the preparation of US '874, or to apply the preparation of US '874 to the pharmaceutical formulation of US '112.

Thus, US '112 and US '874 fail to disclose and/or suggest that the specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent of the present invention can achieve a superior pain relief effect. These patents also fail to contain the requisite motivation/suggestion to combine their teachings to arrive at the claimed invention. Therefore, it would have been difficult for the skilled artisan to ascertain from the teaching of US '112 and US '874 that the specific combination of a local anesthetic and a nonsteroidal antiphlogistic analgesic agent of the present invention can achieve a superior pain relief effect.

In view of the above, the rejection of claims 7-9 under 35 U.S.C. § 103(a) is untenable and should be withdrawn.

**CONCLUSION**

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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**ATTACHMENT TO AMENDMENT AND REPLY:**

1. Declaration under 37 C.F.R. § 1.132 by Mitsuji Akazawa (5 pg.)